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COACH Syndrome: Report of Two Brothers With Congenital Hepatic Fibrosis, Cerebellar Vermis Hypoplasia, Oligophrenia, Ataxia, and Mental Retardation

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Congenital hepatic fibrosis (CHF) is probably the most common cause of non-icteric hepatosplenomegaly and is encountered mainly in children and young adults. We describe here two brothers from healthy, non-consanguineous parents. The patients showed early hepatosplenomegaly, portal hypertension, and no apparent kidney involvement. Clinical and laboratory findings were similar in both patients. Liver biopsies showed the presence of broad septa of fibrous tissue containing abundant bile ducts, portal tracts enlarged by fibrosis, and preserved lobular architecture. The histological findings were suggestive of CHF. Ophthalmological assessment demonstrated visual impairment with mild exotropia, nystagmus, and oculomotor apraxia. Neurological examination showed moderate mental retardation and cerebellar ataxia. Brain MRI confirmed cerebellar malformation with inferior vermis hypoplasia. This pattern of defects is consistent with COACH syndrome (Cerebellar vermis hypoplasia, Oligophrenia, congenital Ataxia, Coloboma, Hepatic fibrocirrhosis) which has previously been reported in five other cases. Our report may contribute to a better delineation of the COACH syndrome phenotype in the spectrum of oculo-encephalo-hepato-renal disorders. © 1996 Wiley-Liss, Inc.

KEY WORDS: COACH syndrome, congenital hepatic fibrosis, cerebellar vermis hypo/aplasia

INTRODUCTION

The term *congenital hepatic fibrosis (CHF)* was introduced by Kerr et al. [1961] to describe fibrosis of the liver as a distinct entity from cirrhosis. CHF is encountered mainly in children and young adults and is probably the most common cause of non-icteric hepatosplenomegaly. The clinical picture of CHF includes hepatosplenomegaly and portal hypertension with normal liver function [Summerfield et al., 1986; Desmet, 1992]. Complications of portal hypertension, including haematemesis due to esophageal varices, hypersplenism, and gastrointestinal haemorrhage, are frequently observed [Fauvert and Benhamou, 1974]. The late appearance of symptoms and their clinical evolution suggest that CHF is a dynamic and progressive condition. Some studies indicate that there is a progressive build-up of liver fibrosis over the years [Lieberman et al., 1971; Gang and Herrin, 1986].

In most, if not all, cases CHF is associated with other congenital abnormalities [Summerfield et al., 1986; Ghishan and Younoszai, 1981]. According to Alvarez et al. [1981], virtually all patients with CHF have polycystic kidney disease. The lack of apparent kidney involvement in young patients might be due to age-related differences in the appearance of clinical signs of the renal dysplasia [Gang and Herrin, 1986; Tazelaar et al., 1984; Matsuda et al., 1990; Proesmans et al., 1986].

Apart from the group of heritable glycogen metabolism disorders, which involve the liver with hepatomegaly, hepatic fibrocirrhosis and progressive liver failure, CHF has frequently been described in combination with ocular abnormalities, renal diseases, cerebellar malformations and mental retardation [Summerfield et al., 1986]. The term *oculo-encephalo-hepato-renal syndrome* is currently employed to report this association. Oculo-encephalo-hepato-renal syndrome is not a single disorder but a group of disorders, including Meckel syndrome [Salonen, 1984], Joubert syndrome [Saraiva and Baraitser, 1992; Lewis et al., 1994], COACH syndrome [Verloes and Lambotte, 1989], Arima syndrome [Matsuzaka et al., 1986], and other different cases [Thomp-

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son and Baraitser, 1986; Stanescu et al.,1986; Casamassima et al., 1987; Labrune et al., 1990]. These syndromes are largely overlapping and accurate classification of individual patients may be difficult.

In view of these difficulties, we report here two sibs from non-consanguineous parents with a COACH syndrome-comparable phenotype. Description of their phenotypes may contribute to better delineate these complex congenital disorders.

CLINICAL REPORTS

Patient 1

The propositus (patient 1) was born in 1978 at the 38th week of gestation after an uneventful pregnancy and uncomplicated breech delivery. Birthweight was 3.6 kg, and head circumference (OFC) 35.5 cm (90th centile). During the first months, his psychomotor development was delayed. The child was generally hypotonic, with difficulty in walking unsupported at the age of 3 years and poorly intelligible speech. Growth was normal, with no respiratory problems.

Physical examination (Fig. 1) showed hypertelorism with abnormal eye movements; frontal bossing; anteverted nostrils with a broad nasal tip; and large, protruding ears. Hepatosplenomegaly was first noticed at the age of 2 years.

At 7 years, abdomen ultrasonography showed a slightly enlarged liver without morphological changes, an enlarged spleen and hyperechogenic pancreas with small vascular dilatations. The description was consistent with portal hypertension. Percutaneous biopsy of the liver (Fig. 2) demonstrated the presence of broad septa of fibrous tissue containing abundant bile ducts, portal tracts enlarged by fibrosis, and preserved lobular architecture without inflammatory cell infiltrates or regenerative nodule formation. The histological findings were suggestive of CHF.

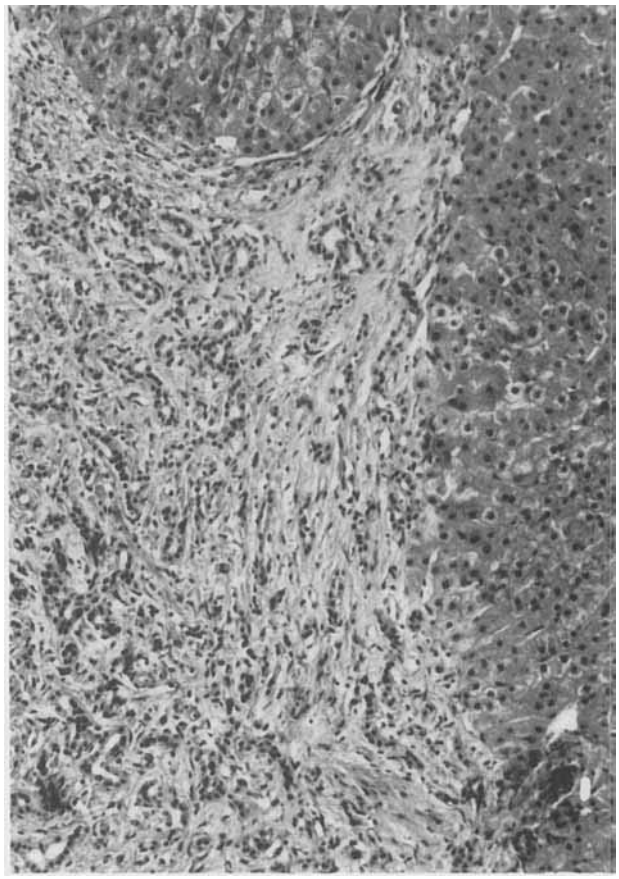

Fig. 2. Patient 1 liver biopsy showing widened portal tracts with dense collagenous fibrous tissue and abundant bile ducts morphologically normal. The hepatocytes are normal. Note the absence of inflammatory infiltrates and regenerative nodule formations.

Fig. 1. Patient 1 at age 10 months.

Muscle biopsy showed a general reduction in size of the fibers. Glycogenosis and congenital myopathies were excluded on the basis of hystochemical and biochemical analysis. Electromyography and nerve conduction were normal.

Ophthalmological assessment confirmed visual impairment with mild exotropia; nystagmus with jerky, symmetrical movements; and oculomotor apraxia. No chorioretinal coloboma was detected at fundoscopic examination. Neurological examination showed severe ataxia with waddling gait, unsteady equilibrium and coordination difficulties, exacerbated by muscular hypotrophy.

At the age of 10 years, he was admitted to hospital for recurrent epistaxis and large haematemesis. Esophagoscopy showed cardial esophageal varices. Abdomen ultrasound and vascular echo-doppler confirmed portal hypertension with hepatosplenomegaly and splenoportal axis enlargement. An electrocardiogram and two-dimensional echocardiography were normal.

The function and ultrasound findings of the kidneys were normal and renal biopsy was not performed. On second liver biopsy histological findings were similar

to, but more pronounced than, those in the first. In addition to the histological examination, fine structure analysis performed by electron microscopy showed multiple layers of hepatocytes characterized by an increased smooth-surface endoplasmic reticulum and increased density mitochondria. No lysosome or peroxisome abnormalities were present.

Brain MRI in axial and sagittal planes showed hypoplasia of the inferior part of the cerebellar vermis without enlargement of the cerebral ventricles or posterior fossa abnormalities suggestive of Dandy-Walker anomaly.

Laboratory investigations indicated hepatic dysfunction with twice the normal levels of serum alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γglutamyl-transpeptidase (γGT). Serum protein electrophoresis showed slightly increased γglobulin. Serum bilirubin, albumin, creatinine, urea, prothrombin time, cooper, ceruloplasmin, and α-1-antitrypsin were normal. Hemolytic complement activity via the classical pathway and the third and the fourth components of the complement were within normal limits.

No anti-nuclear, anti-smooth muscle, anti-ribosome, anti-mitochondrial or anti-reticulin antibodies were found. Serologic tests for hepatitis viruses B (HBV) and C (HCV), human immunodeficiency virus (HIV), and cytomegalovirus (CMV) were negative.

Banded karyotyping at the 500–550 band level of resolution was normal (46, XY). DNA and cytogenetic analysis for fragile X syndrome were negative.

In April 1990, the patient underwent an orthotopic liver transplantation for progressive liver failure. After transplantation he was started on cyclosporin A and prednisolone immunosuppressive therapy, and the postoperative course was satisfactory. Liver function tests were repeatedly normal. Serum markers for hepatitis remained negative until September 1992, when the patient resulted positive for serum antibodies to HCV; the polymerase chain reaction for HCV RNA was also positive.

During the subsequent months he became increasingly icteric (total bilirubin 11.2 mg/dl). In late October 1993, laboratory investigations showed a total bilirubin increase to 16.8 mg/dl (indirect bilirubin 12.3 mg/dl) and elevated ALP (1146 IU/L), ALT (723 IU/L), AST (406 IU/L), and γGT (166 IU/L). Abdominal ultrasonography showed an enlarged liver, irregular in structure, with no focal masses. Liver biopsy confirmed acute HCV infection. Treatment with recombinant interferon was attempted. Initially, the patient's clinical condition and his liver injury tests improved slightly. However, 10 months after the onset of acute hepatitis, he died from hepatic failure. Autopsy was not performed.

Patient 2

The second patient, born in 1991 (birth weight 3.4 kg) at term by cesarean section, is a younger brother of the first patient. At the age of 18 months, the child was admitted to hospital because of delayed milestones in psychomotor development and mild muscular hypotonia.

Like the first patient, he had neither retarded growth nor respiratory difficulties. Neurological examination and the Denver test confirmed global psychomotor delay. EEG was normal. Ocular abnormalities were noticed with sudden symmetrical eye movements, upbeat nystagmus,and difficulties in fixing or following. There was mild exotropia with normal oculomotor and corneal reflexes. Fundoscopic examination excluded optic disk or macular alterations. Physical findings (Fig. 3) included apparent macrocrania with a narrow bifrontal diameter, prominent forehead, mild micrognathia, down-slanting palpebral fissures, saddle-nose, hypoplasia of the dorsal muscles with consequent scoliosis and a palpable liver 2 cm below the right costal margin. Abdomen ultrasonography showed a large liver with no apparent morphological changes but normal spleen and kidneys. No skeletal, cardiac, or pulmonary abnormalities were present. Testicular ultrasonography was normal.

Routine laboratory findings were within normal ranges, including renal and hepatic chemistry, with the exception of mildly raised serum aminotransferases, a great increase in γGT (280 IU/L, normal 40 IU/L), moderate acidosis (serum pH 7.34), and a reduction in B.E. (base excess). Serum cooper was 168 μg/dl (normal 60–140 μg/dl) and ceruloplasmin was 63 mg/dl (normal 20–50 mg/dl).

Laboratory investigations excluded rubella, herpes simplex virus, toxoplasmosis, cytomegalovirus, HBV, HCV, and HIV infections. Serum amino acid chromatography was normal. The urine content of amino acids, organic acids, and oligosaccharides was normal.

The patient underwent further investigations at the age of 30 months. He showed delayed motor and postural organization with difficulty in rising from a chair,

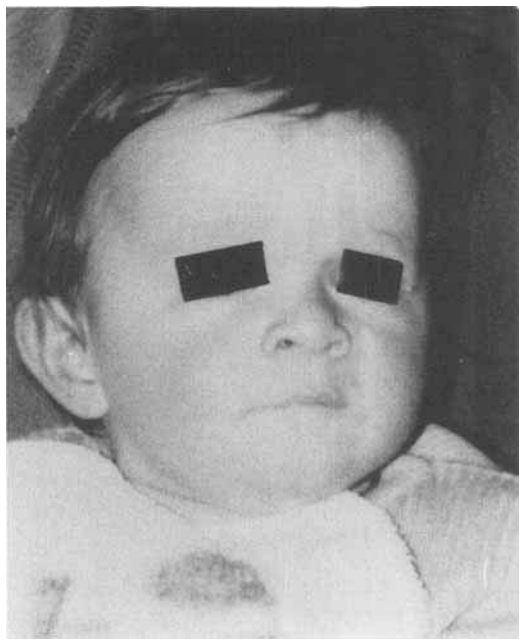

Fig. 3. Patient 2 at age 1 year.

climbing stairs, and walking unsupported. There was moderate psychoneurological retardation with fairly good verbal comprehension, satisfactory manipulation power, and persistent attention. Oculomotor apraxia was present.

Brain MRI (Fig. 4) revealed inferior cerebellar vermis hypoplasia with normal configuration of the fourth ventricle, and mild bilateral signal abnormalities of the subcortical white matter in the frontal and occipital brain regions. No Dandy-Walker malformation (DWM) signs were present. Myelinization was regular for the patient's age.

Abdominal ultrasound findings were unchanged. Liver biopsy showed massive fibrosis without inflammatory infiltration, and morphologically normal parenchyma zones. Although the biopsy specimen only provided small amounts of hepatic tissue for microscopic examination, the pathological changes found were typical of congenital hepatic fibrosis.

Laboratory investigations confirmed liver function impairment. The relevant biochemical test results were as follows: AST 95 IU/L; ALT 161 IU/L; ALP 963 IU/L; γGT 334 IU/L. Renal function tests were normal, while serum cooper and ceruloplasmin were persistently mildly elevated. High-resolution karyotyping gave normal results.

Family Data

The parents were both of Italian ancestry and not related. The mother, born in 1955, was the eldest of five healthy sibs. She had five pregnancies: normal offspring were born from the first and fourth, the second ended in a spontaneous abortion at 2 months, while the third and the fifth pregnancies resulted in patients 1 and 2, respectively.

The father, born in 1951, started to walk with difficulty at 3 years. At the age of 15 he underwent surgical treatment for winged scapula. His mother had died at the age of 20 years from septic abortion. His father had suffered from nervous disorders.

DISCUSSION

Congenital fibrosis is a developmental disorder of the liver and biliary system with variable clinical expression; it can also be observed in association with a heterogeneous group of malformations or syndromes [Summerfield et al., 1986]. The main characteristics of CHF are normal liver parenchyma, fibrosis of the portal spaces, and ductal changes [Jorgensen, 1977]. Parenchymal changes such as atrophy of the liver cells, steatosis, or necrosis may occur, but this does not rule out the diagnosis. The lack of inflammatory infiltrates in the connective tissue differentiates the congenital form of fibrosis from the acquired one. However, the concomitant presence of cirrhosis or recurrent cholangitis can generate some confusion as to the nosological status of the hepatic lesion, making identification of the primary defect difficult. The most typical changes present in CHF are an increased number of bile ducts, localized peripherally in the portal spaces and with different

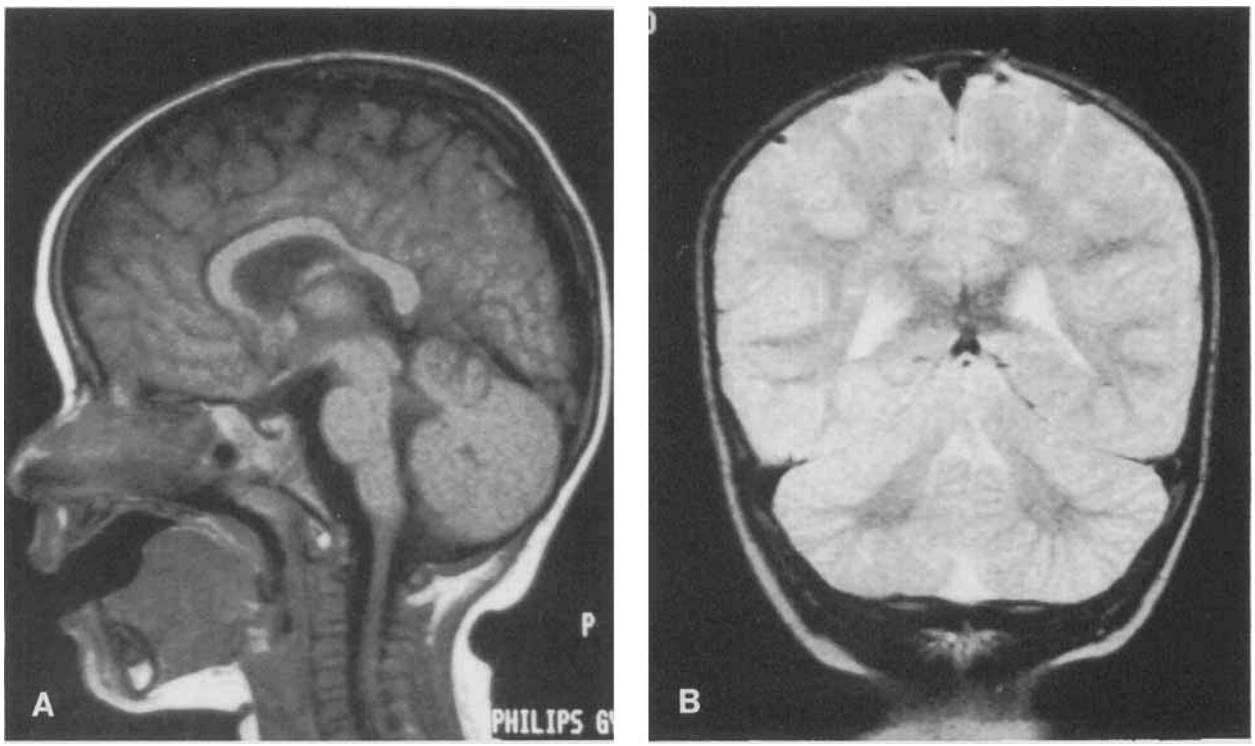

Fig. 4. Brain MRI of patient 2 in sagittal (**A**) and coronal (**B**) planes illustrating mild hypoplasia of the inferior part of the cerebellar vermis without enlargement of the cerebral ventricles.

tubular shapes and a varying degree of flattening; they form an irregular meshwork arranged in planes. Cytologically, the ductal epithelium is well-differentiated and shows no signs of cell proliferation [Desmet, 1992; Fauvert and Benhamou, 1974; Jorgensen, 1977].

The genetic basis of CHF is not clear. Some authors have postulated autosomal recessive transmission [Summerfield et al., 1986] and parental consanguinity has been reported in a few instances [Marinone et al., 1990]. In most cases, CHF is associated with various malformations but due to the perplexing multitude of associations, several authors have suggested that CHF may not represent a single clinical entity [Murray-Lyon et al., 1973].

The two brothers described here presented CHF associated with vermis hypoplasia, ataxia, hypotonia, mild mental retardation, and oculomotor apraxia. The lack of progression of the cerebellar disturbances excludes a degenerative neuronal or glial process, supporting the existence of a congenital malformation involving the inferior portion of the cerebellar vermis. Developmental defects of the cerebellum probably represent a continuum of abnormalities, ranging from cerebellar vermis hypo/aplasia to DWM, which manifests with hypo/aplasia of the cerebellar vermis in association with a posterior fossa cyst, enlargement of the fourth ventricle, and, commonly, hydrocephalus, to tectocerebellar dysraphism with occipital encephalocele [Gardner et al., 1975; Friede, 1978; Casamassima et al., 1987]. These defects, the primary cause of which is unknown and whose pathogenesis is uncertain, seem to arise in the embryonic period in the rostral membranous area where the cerebellar plates meet [Gardner et al., 1975]. In addition, since cerebellar vermis hypoplasia cannot explain some of our patients' symptoms, we assume brainstem involvement as in Saraiva and Baraitser's study [1992]. Abnormal eye movements, speech delay, and mild mental retardation, in particular, are likely due to abnormalities of both cerebellum and brainstem, since anatomical and physiologic evidences indicate large connections between the cerebellum and the reticular activating system [Courchesne et al., 1988].

The series of abnormalities shared by the two brothers provides strong evidence for the presence in both of a distinctive syndrome due to a recessive mutation to a locus exhibiting considerable pleiotropism. A review of the literature elicited several reports in which CHF and/or vermis malformation occur. A striking resemblance exists between our patients and those described by Verloes and Lambotte [1989] and Wiesner et al. [1992] (Table I). The pattern of defects that depicts the COACH syndrome (Cerebellar vermis hypo/aplasia, Oligophrenia, congenital Ataxia, Coloboma, and Hepatic fibrocirrhosis) present in the three children reported by Verloes and Lambotte [1989] and in the two sibs by Wiesner et al. [1992] widely overlaps the one observed in the cases reported here and seems to indicate that we are dealing with the same genetic disorder.

In considering the findings in our patients, one must also take into account the Joubert Syndrome (JS), a rare autosomal recessive condition reviewed by Saraiva and Baraitser [1992]. They summarized 72 previously reported and 29 new patients with the possible diagnosis of JS syndrome. All cases had partial or complete absence of the cerebellar vermis The other cardinal findings were neonatal episodic tachypnea, abnormal eye movements, hypotonia, ataxia, and severe mental retardation. Occasionally additional features have been reported: retinal dystrophy and renal cysts, which delineate a separate group of JS patients first described by Dekaban [1969], as well as coloboma, polydactyly, and occipital meningocele. Our cases fit the diagnostic criteria of JS, presenting all the cardinal findings except for neonatal tachypnea. However, CHF, which is the relevant clinical finding observed in our patients, has been clearly depicted in the context of JS only in two unrelated patients [Lewis et al., 1994].

Fibrotic liver changes have also been included in the diagnostic criteria of Meckel Syndrome (MS), a lethal recessive condition, recently mapped at chromosome 17q21-q24 [Paavola et al., 1995], characterized by a broad clinical inter- and intrafamilial variability [Fraser and Lytwyn, 1981]. Salonen [1984], reviewing 67 cases of MS, proposed cystic dysplastic kidneys, fi-

TABLE I. Comparison of the Clinical Findings in Seven Patients With COACH Syndrome*

Findings	1[a]	2[a]	3[a]	4[b]	5[b]	6[c]	7[c]
Mental retardation	+	+	+	+	+	+	+
Developmental delay	+	+	+	+	+	+	+
Hepatic fibrosis	+	+	+	+	+	+	+
Renal abnormalities	+	−	−	−	+	−	−
Cerebellar vermis hypo/aplasia	+	+	+	+	NS	+	+
Ataxia	+	+	+	+	+	+	+
Hypotonia	+	+	+	NS	NS	+	+
Infantile tachypnoea	−	NS	NS	NS	NS	−	−
Abnormal eye movements	+	NS	+	NS	NS	+	+
Chorioretinal coloboma	−	+	+	+	NS	−	−
Retinal dystrophy	−	−	NS	NS	NS	−	−

*Abbreviations: +, present; −, absent; NS, not specified.
[a]Verloes and Lambotte [1989].
[b]Wiesner et al. [1992].
[c]Present report.

brotic liver changes, and occipital encephalocele or other CNS malformations as minimal diagnostic criteria. Several other reports have focused attention on the presence of cerebellar abnormalities, especially DWM, in association with renal cystic dysplasia and hepatic fibrosis, raising the question as to whether these cases represent MS variants or distinct clinical entities [Miranda et al., 1972; Kudo et al., 1985; Casamassima et al., 1987; Gloeb et al., 1989; Walpole et al., 1991; Herriot et al., 1991; Moerman et al., 1993; Summers and Donnenfeld, 1995]. An atypical borderline patient with phenotypic peculiarities of JS and MS syndrome was investigated by Genuardi et al. [1993]. All these reports provide further evidence of the difficulties in establishing a diagnosis in atypical cases, and suggest that cerebellar malformations, particularly DWM, should be included in the spectrum of CNS abnormalities which may be found in MS. On this basis, CHF and the cerebellar malformation observed in our cases overlap with those observed in some cases of MS, although the latter are distinguished by their poor survival, renal dysplasia, and/or polydactyly.

Apart from the classical and variant forms of MS and JS, the association of bilateral renal cystic dysplasia, biliary dysgenesis, and pancreatic fibrosis defines renal-hepatic-pancreatic dysplasia (RHPD), first described by Iwemark et al. [1959], and successively reconsidered by Bernstein et al. [1987]. Several reports have described additional malformations and syndromes associated with RHPD, addressing the question of whether the RHPD constitutes a variable disease spectrum with a common aetiology, or different aetiological conditions [Bernstein et al., 1987; Breuton et al., 1990; Hunter et al., 1991]. The complex of hepatic abnormalities described in RHPD patients [Bernstein et al., 1987] is quite similar to that observed in our patients; however, poor survival, cystic kidneys, and pancreatic dysplasia, the cardinal and most frequently reported components of RHPD syndrome, are absent in our cases.

Nephronophtisis, hepatic fibrosis, mental retardation, and vermis hypoplasia were described by Dieterich and Straub [1980] in one little girl and, according to family reports, in her sister, who had died 11 years before. Matsuzaka et al. [1986] reported two boys with nonspecific hepatic fibrosis in association with agenesis of the cerebellar vermis, Leber congenital amaurosis, and infantile polycystic kidney disease. The two sisters in Thompson and Baraitser's report [1986] shared congenital hepatic fibrosis, cystic renal dysplasia, and coloboma, but owing to the presence of several clinical discrepancies, it is difficult to consider them as affected by the same syndrome. Finally, Labrune et al. [1990] reported a boy with CHF, cystic kidneys, mental retardation, and abnormal feet and hands. The broad variability of clinical manifestations existing among the patients reported above makes it difficult to ascribe each case to a well-defined syndrome, even if it is possible to group them under the broad heading of long-surviving oculo-encephalo-hepato-renal disorders.

In conclusion, as CHF represents the most relevant clinical feature in our patients as well as those reported by Verloes and Lambotte [1989] and Wiesner et al. [1992], despite the absence of chorioretinal coloboma, we consider them as affected by COACH syndrome. Besides, it should be borne in mind that chorioretinal coloboma has also been reported as an additional finding in the spectrum of abnormalities characterizing JS [Laverda et al., 1984].

From the genetic point of view, the different phenotypes here described could be the consequence of mutations at different loci or represent the spectrum of different mutations of a single gene. Lewis et al. [1994] pointed out that mutations of genes regulating epithelio-mesenchymal interactions could have a role in this overlapping group of syndromes. Thus an important goal for molecular genetics will be to identify the gene(s) involved.

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